abnormalities, wherein the method comprises administering to the patient a therapeutically effective amount of an inhibitor of dipeptidyl peptidase IV.

REMARKS

Claims 21-22 and 24-27, as amended, are pending. Applicants respectfully request confirmation that claims 21-22 and 24-27 are indeed pending, contrary to Examiner's indication (on page 2 of the Office Action) that claims 9-29 are presented for examination. Claim 26 was amended to correct several inadvertent typographical errors, adding the term "scleroris" after the phrase "amyotrophic lateral" and replace the term "a" with "an." No new matter has been added, and support for this amendment may be found, for example, in the Specification at page 7, lines 1-8.

The Claims Are Enabled

The Examiner objected to the specification, and rejected claims 21 and 24, under 35 U.S.C. § 112, first paragraph, for allegedly failing to adequately teach how to make and/or use the invention. Citing *In Re Wands*, the Examiner states that the instant invention could not be practiced by one of ordinary skill in the art without recourse to undue experimentation. *Id.* Applicants respectfully traverse and request reconsideration for the following reasons.

Applicants submit that the Examiner has not established a *prima facie* case of non-enablement. Accordingly, Applicants submit that their application is in full compliance with 35 USC § 112. Section 112 mandates that patent applications contain the "manner and process of making and using" the invention. The courts have considered applications in compliance with section 112 where the person of skill in the art can practice the invention without undue experimentation. *See Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986). The test is not whether experimentation is necessary, but whether any experimentation would be undue in view of what type and amount of experimentation is usual in that particular field. *See* MPEP §§ 2164.05 (a-b), 2164.06 (August 2001). Routine design choices cannot be equated with non-enablement. Moreover, the fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of

experimentation "must not be unduly extensive." *Atlas Powder Co., v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). The proper test is not merely quantitative since some experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. *Ex parte Jackson*, 217 USPQ 804, 807 (1982).

Thus, the burden to establish an enablement rejection rests with the Examiner. *See* MPEP §§ 2164.01; 2164.04 (August 2001). As explained by the Federal Circuit in considering the intertwined issues of enablement and utility:

> [I]t follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the inventor's asserted utility. * * * Taking these facts – the nature of the invention and the PTO's proffered evidence – into consideration we conclude that one skilled in the art would be without basis to reasonably doubt applicants' asserted utility on its face. The PTO has not satisfied its initial burden. *Accordingly, applicants should not be required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of § 112.*

In re Brana, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (emphasis added), *citing In re Marzocchi*, 169 USPQ 367, 369-70 (CCPA 1971). Applicants submit that the Examiner has not met this burden, as explained below.

First, Applicants respectfully point out that the compounds for use in the methods of the invention are characterized functionally by their ability to inhibit, preferably reversibly, DPP-IV. Further, Applicants respectfully submit that there is nothing intrinsically wrong in defining something by what it does rather than what it is. *See, e.g., In re Hallman*, 655 F.2d 212, 210 USPQ 609 (CCPA 1981), *In re Echerd*, 471 F.2d 632, 665 (CCPA 1973), *In re Swinehart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971). In an enablement context, the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. "Nothing more than objective enablement

is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." *In re Wright*, 999 F.2d 1557, 1561 (Fed Cir. 1993). Thus, an enablement rejection only can be supported when the experimentation needed to practice the claimed invention is considered 'undue' by the field. Accordingly, in making a rejection the Examiner must distinguish between routine work and undue experimentation. *See* MPEP § 2164.06 (August 2001).

In the present situation, screening would be practiced by the skilled person in order to obtain compounds that inhibit, preferably reversibly, DPP-IV. The skilled person is provided with a screening approach by applicants' specification. In similar circumstances, the Federal Circuit has considered applications enabling where screening was required. *See In re Wands,* 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (holding an application enabled where there was "considerable direction and guidance" in the specification, "a high level of skill in the art," and the "methods needed to practice the invention were well known."); MPEP § 2164.01(a) (August 2001). These factors inure to applicants' benefit regarding the screening aspects of the present invention.

The instant disclosure provides both one hundred and forty (140) specific examples at pages 23-75, and broad terminology in the form of proper functional limitations that describe with reasonable specificity how to make additional embodiments of the invention across the full scope of the claims: an ability to inhibit, preferably reversibly, the enzymatic activity of dipeptidyl peptidase IV, is what is required of a compound for use in the methods of the invention. Various simple protocols for DPP-IV enzyme inhibition were well-known to one of ordinary skill in the art at the time the present application was filed. For instance, Examples 5 and 6 show exemplary testing protocols for neuroactivity, as well as prostate treatment efficacy in the context of DPP-IC inhibition.

Applicants' disclosure provides one of ordinary skill in the art with sufficient guidance to determine whether a compound is useful in the treatment of a central nervous system disorder. Indeed, Applicants' disclosure provides compounds that inhibit dipeptidyl peptidase IV activity and are deemed useful for the treatment of disorders of the central nervous system, as well as DPP-IV enzyme inhibition assays, which were themselves well-known in the art. A compound that meets that functional limitation, and screened according to Applicants'

teachings can be selected for use in the claimed methods for the treatment of central nervous system disorders. *See, e.g.* Specification at pages. 3-14.

In addition, the process of selection amounts to no more than a simple and straightforward routine screening procedure that would allow for the identification of useful compounds from any pharmaceutical compound library, as would be understood by one skilled in the art. The need for only routine screening should weigh against a determination of undue experimentation, *c.f. Tabuchi v. Nubel*, 559 F. 2d 1183, 1186-7 (CCPA 1977), as should the simplicity of the actual screening procedure, viewed in light of the relatively high levels of skill possessed by those in the pharmaceutical arts.

Accordingly, the claimed compounds may be ascertained by routine experimentation or by the reasonable guidance of the specification and thus, undue experimentation is not necessary.

In view of the Examiner's allegation that Applicants fail to provide a number of working examples sufficient to provide an exhaustive list, or to define the class of compounds required (*See* Office Action at page 3), Applicants reiterate that the instant disclosure (*e.g.*, Specification at pages 15-75) provides one hundred forty (140) widely varying specific examples of compounds useful for the practice of the methods of this invention. Examples of methods for determining the efficacy of inhibitors of dipeptidyl peptidase IV in promoting neurite outgrowth and protection of CNS neurons are disclosed in the Specification at pages 75-77. It is respectfully submitted that, while Applicant's disclosure provides an ample number of examples, the claims presently under rejection do not depend on the number and scope of the disclosed working examples to "define the class of compounds required" (*See*, Office Action, at page 3, line 14). Rather, the compounds for use in the invention are defined functionally through their ability to inhibit, preferably reversibly, the enzymatic activity of DPP-IV.

Applicants further point out that the invention is a pioneering invention, which calls to mind the following statement from the Court of Customs and Patent Appeals:

> For all practical purposes, the board would limit Appellant to claims involving the specific materials disclosed in the examples, so that a competitor seeking to avoid infringing the claims would

> merely have to follow the disclosure in the subsequently-issued patent to find a substitute. However, to provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for " preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

See In re Goffe, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976).

In order to promote the progress of the useful arts, Applicants must be afforded a claim scope as presented so that they can enjoy the " exclusive Right to their ... Discoveries." U.S. Const., art. I, § 8, cl. 8. To do otherwise would permit third parties, who did not contribute to the progress of the useful arts, to enjoy fruits of Applicants' invention unfettered, and thus Applicants would not receive their just reward for their invention.

For any of the above reasons, Applicants respectfully submit that the claims are fully enabled and request that the rejections under 35 U.S.C. §112, first paragraph, be reconsidered and withdrawn.

The Claims Are Not Anticipated

The Examiner rejected claims 21 and 24 as being anticipated under 35 U.S. C. §102(b) by Ronai *et al.* Applicants respectfully traverse and request reconsideration.

In order to reject a claim under 35 U.S.C. § 102, the Examiner must demonstrate that each and every claim term is contained in a single prior art reference. *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 90 (Fed. Cir. 1986); *see also* MPEP § 2131 (August 2001). Claim terms are to be given their plain meaning as understood by the person of ordinary skill in the art, particularly given the limitations of the English language. *See* MPEP §§ 707.07(g); 2111.01 (August 2001). Claims are to be given their broadest reasonable interpretation consistent with applicants' specification. *See In re Zletz*, 13 USPQ2d 1320, 1322 (Fed Cir. 1989) (holding that claims must be interpreted as broadly as their terms reasonably allow); MPEP § 2111 (August 2001).

Ronai does not set forth every element of the rejected claims. In the absence of clear anticipation, the Examiner also provides no explanation of how, or where therein, Ronai recites every element of the rejected claims.

Claim 21 recites a method of treating a patient having a disorder of the central nervous system, which comprises administering to the patient a therapeutically effective amount of a DPP IV inhibitor. Claim 24 recites the additional limitation that the inhibitor be reversible.

To the contrary, Ronai describes a decreased reaction to thermal pain, manifested as increased latency in the tail-flick test, in rats which receive an intracranial injection of Diprotin A. Applicants submit that a method of affecting the normal pain sensitivity of rats with Diprotin A cannot be equated with a therapeutic method of treating a patient having a central nervous system disorder. In other words, pain sensitivity is not a CNS disorder. Accordingly, Ronai fails to disclose each and every element of claims 21 and 24 and Applicants respectfully request that the anticipation rejections be reconsidered and withdrawn.

The Claims Are Not Obvious

The Examiner rejected claims 21-22 and 24-27 under 35 U.S.C. §103 as being obvious in view of Ronai. In particular, the Examiner contends that Ronai teaches a known DPP IV inhibitor as useful in the treatment of CNS pain, viewed by the skilled artisan as a CNS disorder, and that therefore the treatment of migraine would have been obvious. Applicants respectfully traverse and request reconsideration.

At the outset, Applicants note the Examiner must show all of the recited claim elements in the combination of references that make up the rejection. When combining references to make out a *prima facie* case of obviousness, the Examiner is obliged to show by citation to specific evidence in the cited references that (i) there was a suggestion to make the combination and (ii) there was a reasonable expectation that the combination would succeed. Both the suggestion and reasonable expectation must be found within the prior art, and not be gleaned from applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988); *see also* MPEP §§ 2142-43 (August 2001).

When an Examiner alleges a *prima facie* case of obviousness, such an allegation can be overcome by showing that (i) there are elements not contained in the references or within the general skill in the art, (ii) the combination is improper (for example, there is a teaching away or no reasonable expectation of success) and/or (iii) objective indicia of patentability exist (for example, unexpected results). *See U.S. v. Adams*, 383 U.S. 39, 51-52 (1966); *Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d 1923, 1927 (Fed. Cir. 1990); *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve*, 230 USPQ 416, 419-20 (Fed. Cir. 1986).

Applicants respectfully submit that the skilled artisan would not view the somatosensory stimulus under investigation in Ronai as a CNS disorder. An antinociceptive effect in the tail-flick model – a model of peripheral pain – would not lead one of skill in the art to reasonably expect the successful treatment of migraine – a form of central pain – with a DPP IV inhibitor.

Further, assuming *arguendo*, even if the opioid-like effect of the DPP IV inhibitor in Ronai might have some bearing on the treatment of central pain generally, Ronai still does not disclose or suggest anything that would lead the skilled artisan to reasonably expect success in the treatment of central nervous system disorders, much less migraines. In fact, Ronai itself concedes that the biological mechanism by which the investigated DPP IV inhibitor achieved its analgesic effect was entirely unclear (*See* Ronai, at page 146, second paragraph; and at page 151 (discounting presently conceivable mechanisms of action as unlikely, and concluding that the substrate responsible for analgesic effect remained to be identified)), leaving the skilled artisan with nothing but pure speculation as to whether treating central nervous system disorders, much less migraines, would, or would not be, successful.

The Examiner next explains that treating pain collateral to any disease would have been obvious to one skilled in the art (*See* Office Action at page 5, third paragraph), that there would have been a reasonable expectation of therapeutic success for the claimed uses, and that the issue presented in the instant application therefore devolves to the question of obviousness of the "claimed analgesic methods" (Id., at p. 12, 1st paragraph). The Examiner attempts to support this reasoning with an inherency argument.

The instant *obviousness* rejection is unusual because it appears to be premised, at least in part, on properties allegedly *inherent* in the prior art. Obviousness and inherency, however, are different issues. That which may be inherent may not necessarily be known. Obviousness

cannot be predicated on what is unknown." *In re Jones and Hardinger*, 883 F.2d 1026 (Fed. Cir. 1989)(quoting *In re Spormann*, 150 U.S.P.Q. 449, 452 (CCPA 1966).

Applicants respectfully submit that it is indisputable that the treatment of pain with an inhibitor of DPP IV does not "inevitably" result in the treatment of a disorder of the central nervous system. Moreover, ostensibly occasional results are not inherent. *Mehl/Biophile International Corp. v. Milgraum*, 192 F.2d 1362, 1365 (Fed. Cir. 1995).

The limited applicability of the Examiner's inherency argument is further illustrated by the anomalous result that would follow if his position were valid. To cite an example: by the late 1980's, patients suffering from rheumatoid arthritis had been treated for decades with non-steroidal anti-inflammatory drugs ("NSAIDs"). It was then observed for the first time that such patients had a lower incidence of Alzheimer's disease as compared to non-rheumatoid patients. A pilot study with Alzheimer's patients revealed that NSAID treatment indeed appeared to slow the progression of the disorder, and the USPTO subsequently granted that development a patent. *See* U.S. Patent No. 5,192,753 to McGeer *et al.* Under the Examiner's present view, this invention would have been rendered unpatentable by the inevitable fact that some of the millions of patients who had received NSAID therapy for their rheumatoid arthritis prior to this discovery also happened to suffer from Alzheimer's disease, i.e. their CNS disorder had been inherently treated by their arthritis medication.

The Examiner cites to *In re Swinehart*, 169 U.S.P.Q. 226 (CCPA 1971) for the proposition that "the mere recitation of a newly discovered function or property, inherently possessed by things in the prior art, does not cause a claim drawn to those things to distinguish over the prior art." *Swinehart*, however, is distinguishable from the instant case because Applicants do not undertake "the mere recitation of a newly discovered function or property, inherently possessed by things in the prior art". For any of the above reasons, Applicant's novel method of treating CNS disorders is not "inherently possessed" in the antinociceptive method of Ronai. Accordingly, Applicants respectfully request that the rejections obviousness rejection be reconsidered and withdrawn.

Request

Applicants submit that the claims are in condition for allowance, and respectfully request favorable consideration to that effect. The Examiner is invited to contact the undersigned at (202) 912-2000 should there be any questions.

Respectfully submitted,

Date: August 2, 2002

Heller Ehrman White & McAuliffe LLP
1666 K Street, N.W., Suite 300
Washington, D.C. 20006-4004
Telephone: (202) 912-2000
Facsimile: (202) 912-2020

John P. Isacson
Attorney for Applicant
Reg. No.: 33,715

Customer No. 30147

MARKED-UP COPY OF AMENDED CLAIM

26. (Amended) A method of treating a patient having a disorder selected from the group consisting of strokes, tumors, ischemia, Parkinson's disease, memory loss, hearing loss, vision loss, migraines, brain injury, spinal cord injury, Alzheimer's disease, amyotrophic lateral **sclerosis**, multiple sclerosis, diabetic neuropathy and prostate abnormalities, wherein the method comprises administering to the patient a therapeutically effective amount of **an** **[a]** inhibitor of dipeptidyl peptidase IV.